Amendments to the Specification

Please amend the specification as follows:

Please insert the following heading on page 1 after the title and before the first paragraph:

This application is a National Stage application of PCT/EP2004/004076, filed April 16, 2004, which claims priority from European patent application 03008753.0, filed April 17, 2003, and European patent application 03019626.5, filed September 4, 2003. The entire contents of each of the aforementioned applications are incorporated herein by reference.

Background of the Invention

Please insert the following heading on page 4 between the third and fourth complete paragraphs:

Summary of the Invention

Please insert the following headings and paragraphs on page 6 before the first full paragraph beginning with "It has surprisingly been found...":

The present invention further relates to a vector and a host cell containing the nucleic acid molecules described herein as well as methods of using such hosts to produce polypeptides encoded by the nucleic acid molecules. In this regard, the present invention also relates to the polypeptides encoded by the nucleic acid molecules and antibodies that specifically bind to the polypeptides.

The present invention additionally relates to an aptamer that specifically binds to a nucleic acid molecule as described herein and a primer or a pair of primers that are capable of specifically amplifying a nucleic acid molecule described herein.

The present invention further relates to methods of diagnosing or diagnosting a susceptibility to an affective disorder or methods of treating an affective disorder as described within the present invention. Diagnostic and pharmaceutical compositions comprising nucleic acid molecules, compounds, modulators and/or agonists as described herein that are useful for these purposes.

Detailed Description of Figures

The Figures show:

Figure 1a. Genomic map of the region on the human chromosome 12 associated to bipolar affective disorder. Genes found between markers NBG11 and NBG2 are depicted.

Figure 1b. Graphic illustrating the multipoint analysis using ASPEX on independent sib-pairs.

Figure 1c. Graphic illustrating the multipoint analysis using ASPEX on all sib-pairs

Figure 1d. Graphic illustrating the ASPEX sib_phase by considering only independent sib-pairs

Figure 1e. Graphic illustrating the ASPEX sib_phase by considering all sib-pairs

Figure 1f. Effect of the P2XR7v13A polymorphism on basal cortisol levels before and after administration of dexamethasone (DST test). Individuals were subjected to the test within the first ten days of admission. Individuals with the AG and GG genotypes have significantly lower cortisol levels pre- and post-dexamethasone administration.

Figure 1g. Effect of the P2XR7v13A polymorphism on cortisol response during the Dex/CRH test. Individuals were subjected to the test within the first ten days of admission (i.e. At admission) and at the last ten days before discharge (i.e. at discharge). Individuals with the GG genotype have lower cortisol levels in response to the Dex/CRH test at admission and at discharge. These results are indicative of an abnormal HPA axis.

Figure 1h. Effect of the P2XR7v13A polymorphism on ACTH response during the Dex/CRH test. Individuals were subjected to the test within the first ten days of admission (i.e. at admission) and at the last ten days before discharge (i.e. at discharge). Individuals with the GG genotype have lower ACTH levels in response to the Dex/CRH test, at admission and at discharge. These results are indicative of an abnormal HPA axis.

Figure 1i. Duration of antidepressant treatment until remission. Depression is diagnosed according to the Hamilton Depression Rating Scale (HAM-D; Hamilton, Br. J. Soc. Clin. Psychol. 6 (1967) 278-296). A HAM-D score of 10 or below is regarded as remission of the depressive symptoms.

Figure 1j. Effect of the P2XR7v13C polymorphism on basal cortisol levels before and after administration of dexamethasone (DST test). Individuals were subjected to the test within the first ten days of admission. Individuals with the CC genotypes have elevated cortisol levels post-dexamethasone administration.

Figure 1k. Effect of the P2XR7v13C polymorphism on cortisol response during the Dex/CRH test. Individuals were subjected to the test within the first ten days of admission (i.e. at admission) and at the last ten days before discharge (i.e. at discharge). Individuals with the AC or CC genotype have elevated cortisol levels in response to the Dex/CRH test at admission, indicating an abnormal HPA axis.

Figure 1l. Effect of the P2XR7v13C polymorphism on ACTH response during the Dex/CRH test. Individuals were subjected to the test within the first ten days of admission (i.e. at admission) and at the last ten days before discharge (i.e. at discharge). Individuals with the CC genotype have lower ACTH levels in response to the Dex/CRH test, at admission and at discharge. These results are indicative of an abnormal HPA axis.

Figure 2. RT-PCR analysis of the complete coding sequence of P2X7R in different tissues

Figure 3. P2X7R expression in the olfactory bulb, hypothalamus and ependymal cells in the brain of a stress-free mouse. Magnification 100X.

Figure 4. P2X7R expression in the hippocampus/dentate gyrus and subcommisural organ in the brain of a stress-free mouse. Magnification 100X.

Figure 5. Floating behaviour in the forced swim test. Passive stress coping behaviour decreased after long-term treatment with the antidepressant paroxetine (Par28: treated with paroxetine for 28 days, per os). Basal n=8; vehicle n=8; Par28 n=8.

Figure 6. Comparative analysis of P2X7R expression in the olfactory bulb of stress-free, vehicle-treated and antidepressant-treated mice. Magnification 100X.

Figure 7. Comparative analysis of P2X7R expression in the hypothalamus of stress-free, treated-treated and antidepressant-treated mice. Magnification 100X.

Figure 8. Comparative analysis of P2X7R expression in ependymal cells of stress-free, vehicle-treated and antidepressant-treated mice. Magnification 100X.

Figure 9. Comparative analysis of P2X7R expression in the hippocampus of stress-free, vehicle-treated and antidepressant-treated mice. Magnification 25X.

Figure 10. P2X7R expression in the hippocampus of a vehicle treated mouse. Magnification 25X.

Figure 11. P2X7R expression in the hippocampus of a mouse treated with the antidepressant paroxetine. Magnification 25X.

Figure 12. Detailed expression of P2X7R in the dentate gyrus of a mouse treated with the antidepressant paroxetine. Magnification 400x.

Figure 13. Comparative analysis of P2X7R expression and apoptotic cells in the hippocampus of à mouse treated with the antidepressant paroxetine. Magnification 100X.

Figure 14. Floating behaviour in the forced swim test. Passive stress coping behaviour increased after acute intrahippocampal (bilateral, dentate gyrus) of siRNA targeting P2X7R. Vehicle n=7; control RNA n=10; P2X7R siRNA n=9.

Figure 15. Comparative analysis of P2X7R expression in the hippocampus of mice treated with vehicle, control RNA and of siRNA targeting P2X7R. Magnification 100X upper row, 25X lower row.

Figure 16a, b, c, d, e. Three splicing variants caused by polymorphisms in the introns of P2X7R.

Figure 17. Expression of P2X7R in immortalized hippocampal cell lines.

Figure 18. Increase calcium influx in hippocampal cells treated with a P2X7R agonist compound (BzATP).

Figure 19a, b. Entry of ethidium bromide dye into hippocampal cells (a) treated with P2X7R agonist compound (BzATP) or (b) pre-treated with a P2X7R antagonist compound.

Figure 19c. Agonist action of BzATP and tenidap on P2X7R activity. The calcium channel activity of human P2X7R was measured under basal conditions for four seconds to 10 seconds. A. Negative control consisting of cells loaded with 10 μM Fluo-4-AM without further treatment. B. Cells treated with 20 μM BzATP after four seconds of basal measurement. C. Cells treated with 50 μM tenidap after four seconds of basal measurement.

Figure 20. Effect of intrahippocampal injection of a P2X7R agonist compound (BzATP) on behaviour in the forced swim test.

Figure 21. Open field test measuring locomotor activity of mice treated with a P2X7R agonist compound (BzATP).

Figure 22. Comparative analysis of apoptotic cells in the hippocampus of a mouse treated with control vehicle solution or a P2X7R agonist compound (BzATP).

Figure 23. Effect of intrahippocampal injection of the P2X7R antagonist KN-62 and oATP on behaviour during the forced swim test

Figure 24. Open field test measuring locomotor activity of mice treated with the P2X7R antagonist KN-62 and oATP.

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